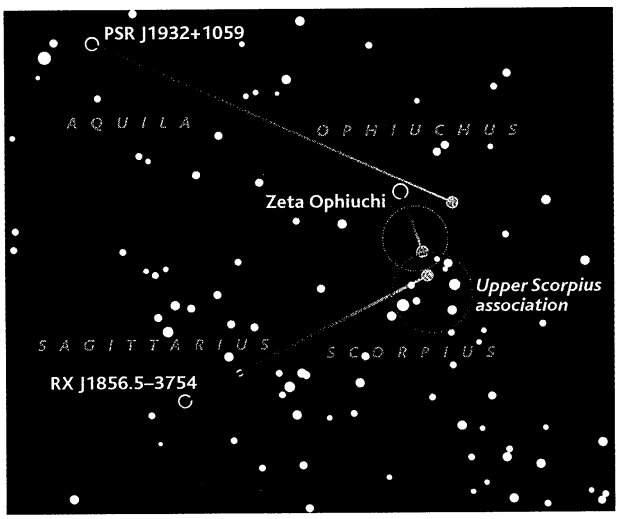
ASTROPHYSICS

Neutron Stars Linked To Celestial Runaway

A million years ago, in the constellation Scorpius, one of a pair of binary stars erupted into a supernova. Its nonexploding partner shot off into space and is now Zeta Ophiuchi, a bright, giant "runaway star" racing through the neighboring constellation Ophiuchus. The supernova has been harder to trace. Astrophysicists know it must have collapsed into a neutron star, but where it wound up has been anyone's guess. Now, however, astronomers are fingering two candidates, one of which is the closest known neutron star to Earth. The discovery, if confirmed, will give astronomers a better understanding of the dynamics of supernova explosions in binary systems and the origin of runaway stars.



Hindsight. Tracing star positions (red) back 1.15 million years (blue) pairs two possible partners with Zeta Ophiuchi.

The nearby neutron star, known as RX J1856.5–3754, was first detected by the German ROSAT x-ray satellite, and it was spotted in visible light in 1997 by Fred Walter and Lynn Matthews of the State University of New York, Stony Brook, using the Hubble Space Telescope. New Hubble images, taken in March and September 1999, enabled Walter to calculate both the faint star's distance from Earth—a mere 200 light-years—and its proper motion, or apparent path across the sky. Traced backward, Walter says, "the proper motion brings the neutron star from the general vicinity of the Upper Scorpius association"—the group of bright, young stars in which Zeta Ophiuchi was born.

In a paper scheduled for publication in the 10 January 2001 issue of *The Astrophysical Journal*, Walter theorizes that RX J1856.5–3754 is the collapsed core of the supernova that flung Zeta Ophiuchi into space. Because the neutron star's radial velocity (its movement toward or away from Earth) is unknown, astronomers can't tell whether the path leads into the association or passes in front of it. But Walter calculates that if the neutron star came from the association, it did so 1.15 million years ago—just when Zeta Ophiuchi made its own explosive exit. That timing matches evidence of the star's youth, Walter says. Lone neutron stars are expected to cool down over time, yet RX J1856.5–3754's x-ray brightness indicates that its surface is blazing away at more than 500,000 K. Such a hot neutron star, he concludes, must be young.

Some other astronomers, however, believe RX J1856.5–3754 may be far too old to have been Zeta Ophiuchi's companion. Marten van Kerkwijk of Utrecht University in the Netherlands and Shri Kulkarni of the California Institute of Technology in Pasadena announced this week that observations with the European Southern Observatory's Very Large Telescope in Chile show that RX J1856.5–3754 is trailing a small, faint cone of glowing hydrogen gas, supposedly heated by the star's intense x-rays. From the brightness of the glow, the scientists calculate that the gas near RX J1856.5–3754 must be about 100 times as dense as the galactic average. The gas would slam onto the compact star at half the speed of light, heating the surface and making it appear younger than it actually is.

With so much matter available to heat it, Van Kerkwijk says, RX J1856.5–3754 could well be billions of years old—thousands of times too ancient to have been born in Upper Scorpius. But Walter argues that if the star is that old, it would have attracted enough interstellar hydrogen to make its visible light hundreds of times brighter than astronomers observe.

Van Kerkwijk thinks a much more likely candidate for Zeta Ophiuchi's erstwhile partner is a radio pulsar known as PSR J1932+1059. Pulsars are spinning neutron stars that emit radio pulses. From the rate at which PSR J1932+1059's rotation is slowing down, Van Kerkwijk calculates that the pulsar is at most a few million years old. In another *Astrophysical Journal* paper, scheduled to appear in October, Ronnie Hoogerwerf, Jos de Bruijne, and Tim de Zeeuw of Leiden Observatory in the Netherlands show that PSR J1932+1059 also left the Upper Scorpius association 1 million years ago, assuming that its radial velocity—also unknown—is about 200 kilometers per second.

Walter agrees that PSR J1932+1059 could be the former binary companion of Zeta Ophiuchi. But he believes RX J1856.5–3754 is young enough to be a candidate as well. In any case, Walter says, it's perfectly possible that the hot neutron star and the young pulsar flared into being in the same part of the sky at about the same time. "There was at least one supernova in Upper Scorpius about 1 million years ago. Why not two?" **–GOVERT SCHILLING**

Govert Schilling is an astronomy writer in Utrecht, the Netherlands.

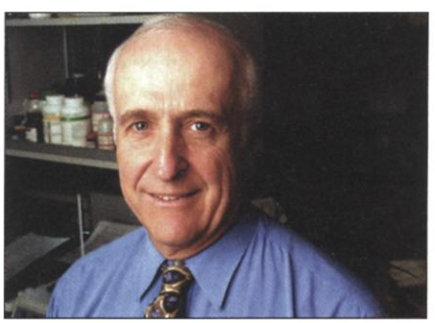
APPOINTMENTS

Salk Institute Goes North for New CEO

The revolving door at the top of the Salk Institute for Biological Studies in La Jolla, California, took another spin last week with the appointment of neuroscientist Richard Murphy as president and CEO. Murphy, director of the Montreal Neurological Institute (MNI), will become Salk's fourth chief executive in 4 years when he takes up the reins on 1 October. Murphy, 56, says his main job will be to raise enough money to keep the endowment-poor research institute in the scientific big leagues.

Founded in 1960 by polio vaccine developer Jonas Salk, the institute has become a dominant player in molecular biology and genetics. But Salk executives have had a difficult time translating scientific success into long-term financial health. Part of the problem is that Salk, dedicated exclusively to research, does not graduate students and is therefore not blessed with generous alumni. More recently, however, the institute's frequent changes in leadership have created another problem—a suggestion that the institute lacks a clear sense of direction.

Born and trained in the United States, Murphy says that he doesn't plan to run a research group at Salk and that "this will be a full-time job with all the fund raising involved." At MNI he raised more than $25



Money man. Richard Murphy says his top priority is to boost Salk's endowment.

CREDITS: (LEFT TO RIGHT) G. SCHILLING AND A. STONEBRAKER; SALK INSTITUTE

million during his 8-year tenure, allowing the institute to hire 20 new faculty members and carry out needed renovations. "He rejuvenated that institute," says Salk molecular biologist Tony Hunter.

The need to raise money isn't a new task for the head of Salk, of course. Murphy's immediate predecessors, Salk structural biologist Thomas Pollard and current CEO Frederick Rentschler, managed to boost Salk's endowment from under $50 million in 1996 to $120 million today, although Pollard stepped down as CEO a year ago to focus on his research. Even with that success, Salk's endowment is only one-tenth the size of those of similar places like the Rockefeller University in New York City, notes Charles Stevens, a Salk neuroscientist and member of the search committee that tapped Murphy.

Large endowments allow top-tier research institutes to pay for expensive equipment such as gene chip arrays for genetics and nuclear magnetic resonance machines for structural biology, says Hunter. Not having that pot of money, he adds, "makes it harder for us to compete." It also prevents Salk from providing much salary support for its 54 faculty members and puts it at a disadvantage in recruiting, says Stevens.

Hunter, Pollard, and others are optimistic that Murphy can keep Salk in the race. "It's a terrific selection," says Pollard. And although Salk's scientific luster doesn't need much polishing, Hunter hopes that Murphy's arrival will also stop the revolving door: "We would love to have someone who sticks around for a while." **–ROBERT F. SERVICE**

With reporting by Wayne Kondro in Ottawa.

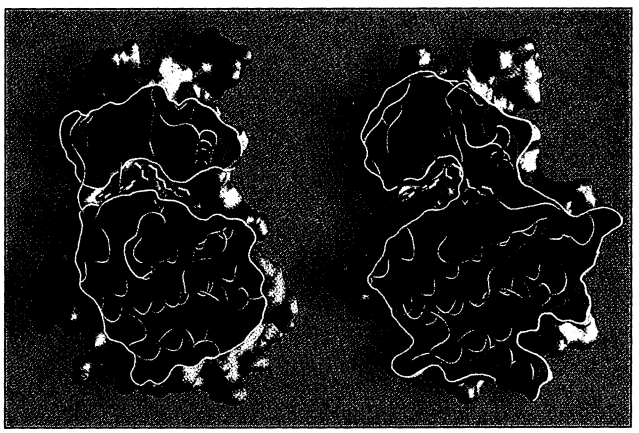
MOLECULAR BIOLOGY

Cancer Fighter's Modus Operandi Revealed

Researchers have deciphered how a promising cancer drug acts like a smart bomb, homing in on only a very narrow range of its potential targets in the cell. The compound, known as STI-571, has shown remarkable success in early clinical trials on patients with chronic myelogenous leukemia (CML). Now, in work reported on page 1938, John Kuriyan and Thomas Schindler of the Rockefeller University in New York City and their colleagues reveal just how the compound works—information that could aid in the design of similar cancer therapies. "It's a very neat story," says cell biologist Tony Hunter of the Salk Institute for Biological Studies in La Jolla, California.

Scientists already knew that STI-571 blocks the enzyme produced by the *abl* oncogene, whose activation has been linked to the massive proliferation of leukemia cells in CML patients. They have been hard put to explain, however, why the compound doesn't also block closely related enzymes. The *abl* oncogene is one of hundreds of genes identified over the past 25 years that can, when abnormally active, lead to cancer. The hope is that the proteins made by these oncogenes will provide good drug targets. But many oncogenic proteins, including the Abl protein, belong to one of the largest enzyme families in the cell—the protein kinases, which transfer a phosphate group from ATP to proteins. Thus any effort to snuff out an aberrant kinase could easily produce a great deal of collateral damage and unacceptable side effects for cancer patients.

But STI-571 is a notable exception. It was identified in the early 1990s by scientists at the pharmaceutical company Novartis, who found that it inhibits the kinase that acts as the receptor for platelet-derived growth factor. Subsequent tests by Brian Druker's group at the Oregon Health Sciences University in Portland showed that the compound, a small 2-phenylaminopyridine, also inhibits the oncogenic form of Abl and the c-kit kinase, but none of the 50 or so other kinases screened.



Locked up tight. The drug STI-571 (in yellow) binds to the inactive form of the Abl protein, shown at left. But as depicted at right, the drug doesn't fit the active form of Src, another oncogenic kinase.

The discovery that STI-571 blocks Abl activity raised the possibility that it might be used to treat CML. Bone marrow transplants offer a potential cure, but suitable donors can be found for only one-third of patients. And current drug therapies, usually with interferon α, only control the disease for a few years before it eventually progresses to the acute—and fatal—stage. One of the diagnostic hallmarks of this cancer is an abnormal chromosome—the so-called Philadelphia chromosome—formed when a portion of chromosome 22 fuses with the chromosome 9 segment bearing the *abl* gene. As a result, a portion of the *bcr* gene becomes attached to *abl*, and for reasons that are poorly understood, the hybrid protein produced by this fusion gene shows increased kinase activity. What's more, work in animals has shown that the Bcr-Abl protein is all that it takes to cause leukemia.

In the past 2 years, Druker has coordinated a series of trials to determine whether STI-571 does in fact help CML patients, and so far the work looks very promising. For example, at last year's meeting of the American Society of Hematology, he presented the results of a phase I clinical trial—which is primarily aimed at determining tolerable doses—involving 54 patients who no longer responded to interferon α. The cancer cells seemed to disappear from the blood of all 31 of the patients who got doses of 300 milligrams and above, Druker says. What's more, 30 of those patients have remained in remission for about a year of follow-up, and they have reported only mild side effects including some nausea, diarrhea, and muscle cramping.

Druker and his colleagues have since concluded enrollment in a phase II trial to test STI-571's efficacy and have embarked on a phase III trial pitting the drug against standard CML treatments. Researchers familiar with the trials are already enthusiastic. "I can certainly say the results are terrific. It's a home run," says Owen Witte of the University of California, Los Angeles, School of Medicine, whose own work was instrumental in showing Abl's importance in CML. James Griffin, a leukemia expert at Harvard Medical School in Boston, agrees, predicting that "this is going to change the way we treat CML."

The Rockefeller team's work now explains how STI-571 homes in on the Abl kinase. The researchers crystallized the catalytic region of the human Abl protein together with an STI-571 variant. They then used x-ray crystallography to determine the three-dimensional structure of the drug-protein complex. Abl, like many other kinases, has an "activation loop" that has to have a phosphate group added before the enzyme can add phosphate groups to other proteins. This alters the shape, or conformation, of the enzyme, opening it up so that the kinase can bind ATP and its target proteins. What the crystal structure reveals, Kuriyan says, is that STI-571 binds to the inactive conformation of Abl.

This presumably prevents it from acquiring the activating phosphate, thus locking Abl in its inactive conformation, a mode of action that Witte says "makes good sense with how [STI-571] works in the leukemia." Targeting the inactive conformation also explains why

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